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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	P03592US0	*Total Pages*	
First Named Inventor or Application Identifier	Eric M. Weaver		
Express Mail Label No.	EL133867555US		

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. [X] Specification [*Total Pages* 26] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) *(35 USC 113)* [*Total Sheets*]
4. Oath or Declaration [*Total Pages* 2]
   a. [X] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed) [Note Box 5 below]*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. [ ] Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [X] Information Disclosure Statement (IDS)/PTO-1449 [X] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. [X] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [X] Other: Certificate of Mailing.

17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information:*
[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No: _____/_____

18. CORRESPONDENCE ADDRESS

[ ] *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or [X] *Correspondence address below*

NAME	Heidi S. Nebel, Reg. No. 37,719				
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Patent fees are subject to annual revision on October 1.
These are the fees effective October 1, 1997.
Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.
See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT ($) 428.00

Complete if Known	
Application Number	
Filing Date	December 11, 1998
First Named Inventor	Eric M. Weaver
Examiner Name	
Group / Art Unit	
Attorney Docket No.	P03592US0

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

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Deposit Account Name:

[X] Charge Any Additional Fee Required Under 37 C F R §§ 1 16 and 1 17
[ ] Charge the Issue Fee Set in 37 C F R § 1 18 at the Mailing of the Notice of Allowance

2. [X] **Payment Enclosed:**
[XX] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	380.
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 380.

2. EXTRA CLAIM FEES

		Extra Claims		Fee from below	Fee Paid
Total Claims	21	-20** = 1	X	9	= 9
Independent Claims	4	- 3** = 1	X	39	= 39
Multiple Dependent					=

**or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	82	209	41	** Reissue independent claims over original patent
110	22	210	11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 48.

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,320	241	660	Petition to revive - unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($)

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Wendy K. Hartung			Reg Number	39,705
Signature	Wendy K. Hartung	Date	12/11/98	Deposit Account User ID	

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Applicant or Patentee: Eric M. Weaver and Daniel U. Thomson
Serial No. or Patent No: _____
Filed or Issued: _____
For: WATER-SOLUBLE GLOBULIN CONCENTRATE FOR IMPROVING GROWTH IN ANIMALS

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am

[ ] the owner of the small business concern identified below:
[X] an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN LG Laboratories
ADDRESS OF CONCERN 2501 North Loop Drive, Suite 800, Ames, Iowa 50010

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled WATER-SOLUBLE GLOBULIN CONCENTRATE FOR IMPROVING GROWTH IN ANIMALS by inventor(s) Eric M. Weaver and Daniel U. Thomson, described in

[X] the specification filed herewith.
[ ] application Serial No. _____, filed _____.
[ ] Patent No. _____, issued _____.

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights in the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

**NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).*

FULL NAME _____
ADDRESS _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of payment, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME AND TITLE OF PERSON SIGNING Nix Lauridsen, President
ADDRESS OF PERSON SIGNING LG Laboratories, 2501 North Loop Drive, Suite 800, Ames, Iowa 50010

SIGNATURE _____ 12/9/98 DATE _____ 12/9/98

INVENTOR: Eric M. Weaver
Daniel U. Thomson

TITLE: WATER-SOLUBLE GLOBULIN CONCENTRATE FOR IMPROVING GROWTH IN ANIMALS

FIELD OF THE INVENTION

This invention relates to a composition and method for treating piglets and other livestock. Specifically, this invention relates to the treatment of animals with a water-soluble immunoglobulin product post weaning.

BACKGROUND OF THE INVENTION

Piglets are born without the ability to fight disease. Pigs are dependent upon colostrum and later milk from the sow to provide immunoglobulins which confer passive immunity to disease for the first 2 to 3 weeks of life and help "tide them over" until their own immune systems begin functioning. The piglet's endogenous immune system begins to function and produce antibodies in response to environmental stimuli at approximately 2 weeks of age. However, the pig's immune system is not fully competent until about 5 to 6 weeks of age. Until then the pig is susceptible to many biological challenges.

Colostrum contains rapidly diminishing levels of immunologically active, large molecular weight proteins known as immunoglobulins. These immunoglobulins (Ig) possess antibody properties and enhance the pig's immunity to infection by organisms such as bacteria, viruses, and parasites. For various reasons, however, the piglet does not receive adequate amounts of immunoglobulins to impart the

necessary immunity. These reasons include problems at lactation, extra large litters, litter competition, poor nursing sows, low birth weight, and sow death. This decreased immunity causes the piglets to become more susceptible to contracting various bacterial, viral, and parasitic infections, which can cause an increase in mortality from diarrhea and dehydration.

In addition to an immature immune system and a deficiency in immunoglobulins, the animals are often affected by environmental and health stress, which also weakens the animals and causes increased susceptibility to disease and various other health problems, including decreased growth and weight gain. Traditionally, these occur during the early growth and weaning period and include stress from the actual weaning process, shipping, heat, social stresses, and various challenges to the animals' health. This weakened condition is often caused by inadequate feed intake and the inability of the animal to assimilate nutritional elements from the intestine. Undigested nutrients will end up in the large intestine as a substrate for undesired intestinal bacteria flora which causes diarrhea in the animal, further complicating the post-weaning performance of the pig.

The mortality from birth to weaning in normal pig production is generally 12 to 15% but can be as high as 20 to 25% in stressed pig populations. Many of these piglets that die are the object of intense care as they are already underweight and under stress after birth. When the young pig is weaned this is an additional stress factor, especially so

for the lightest pigs of the litter due to the reasons listed above.

At birth, pigs have limited enzyme systems efficient only for digestion of milk. The amount of lactase, the enzyme that breaks down and digests milk sugar, is high during the first few weeks of life but then decreases shortly after weaning. Meanwhile, proteolytic and amylolytic enzymes needed for grain digestion are not fully developed until 4 to 7 weeks of age. Thus, feed stuffs other than milk cannot be efficiently digested and absorbed until the animal is several weeks old. Further, the stress brought about by abrupt changes in diet and environment are stressful on an animal's digestive system, further aggravating the delicate balance of the system.

Current means for improving growth and reducing post-weaning morbidity in animals include the inclusion of plasma to the animals' diet. Such plasma sources have included spray-dried animal plasma (SDAP). The inclusion of spray-dried animal plasma in the diet improves feed intake, weight gain, and the efficiency of gain when compared to other protein sources such as dried skim milk, whey protein concentrate, soy protein, fishmeal, potato protein, and dried egg products. The immunoglobulin component of SDAP is recognized as the factor that improves growth in weaned pigs.

Spray-dried animal plasma is also utilized commercially in milk replacement products (milk replacers) for pigs, calves and sheep. Milk replacers are typically dry powders containing milk by-products (whey, dried skim milk, whey

protein concentrate), soluble, further processed grain products (soy protein concentrate or wheat gluten), fats and oils and appropriate vitamin and mineral fortification. Research has shown that the use of milk replacers fortified with SDAP derived from whey (or colostral whey) results in faster weight gain and reduced morbidity and mortality in calves and pigs. Thomson, D.U., Weaver, Eric M. (1997), "Using Blood Proteins in Calf Milk Replacers," Large Animal Practice, Vol. 18, No. 6, p. 16. Large Animal Practitioner. The administration of SDAP in milk-replacers has several drawbacks, however.

First, milk replacers which include SDAP are usually provided to pigs or calves through a self-contained feeding system of some type. The feeding systems vary in complexity from a bottle with a nipple to automatic feeding devices. SDAP contains fibrinogen, a water soluble protein, which is activated by very low concentrations of calcium to form fibrin, an insoluble protein matrix. Most sources of tap water contain enough calcium to initiate the activation of the conversion of fibrinogen to fibrin. If the concentration of spray-dried animal plasma in a milk replacement product is high enough and the material is given enough time to form a protein matrix, the resulting gel will plug most feeding devices. While various anticoagulants can be used at high levels to prevent activation of the clotting process, such a level of anticoagulants may have undesirable effects on the animal either by decreasing the availability of beneficial

minerals, increasing the osmotic load, or interfering with the blood clotting process in the animal.

Second, milk replacers are expensive and difficult to administer to young pigs, especially those containing significant concentrations of spray-dried animal plasma. Such products are normally prepared between 2-4 times per day in small quantities. Modern swine production is labor-intensive, and these businesses find it difficult to find and keep employees. The addition of labor-intensive production methods, i.e. feeding milk replacement products to the pigs 2-4 times daily, is often not feasible due to the lack of available farm staff.

Further, commercially available milk replacement products usually contain greater than 10% crude fat. This level of fat accumulates and plugs the water lines unless it can be completely removed from the system. Yet another major drawback with milk replacement feeding systems is that the feeding devices must be thoroughly cleaned and disinfected daily to prevent bacterial contamination.

Moreover, although the addition of SDAP to the starter diet of piglets has made it much easier to feed and manage young pigs (less than 21 days of age), it still has not proven to be completely successful in managing the light-end group of pigs, which comprise the bottom 10% of the population. This weight difference at weaning between the heaviest and lightest pigs often leads to greater differences in body weight between the heaviest and lightest pigs at the end of the nursery phase and at slaughter. Such pigs consume

very little feed from 0 to 2 days post-weaning. The presence of SDAP in the feed does little to improve the health of the gut in these very small or young pigs since they do not consume adequate concentrations of feed for 2 days post-weaning. The resulting effect in these pigs is temporary gut atrophy, loss of absorptive capacity, an increase in intestinal permeability and bacterial colonization and translocation.

Elliot et al. describe formulations for milk replacement for artificial rearing of neonatal pigs. (U.S. Pat. No. 4,623,541). The formulations include purified immunoglobulins which are subsequently commingled with condensed skim milk and spray dried. The Elliot formulations are problematic, however, since the procedure for separating the immunoglobulins from the blood involves the use of high levels of ammonium sulfate. While ammonium sulfate is satisfactory for small batches of blood, it is not useful for large-scale separation operations due to problems in disposing of this environmentally hazardous compound. In addition, the Elliot process is not economical to use due to its low yields of immunoglobulin powder.

Newson et al. (U.S. Pat. No. 4,096,244) describe the administration of a composition containing active immunoglobulins to newborn piglets by feeding. An important feature of this invention is the reduction of the saline content of the blood serum to increase the palatability of the serum to the pigs. The invention also emphasizes the administration of immunoglobulins to newborn piglets by

feeding and describes a feed composition similar to milk replacer. The Newson formulation is not economical to use since it is difficult to administer on a large-scale basis and does not provide for the needs of the newly-weaned pig.

There is therefore a need in the art for a supplement for young pigs (>2 days of age) which is economical and convenient to use on a large scale basis, yet also effective for administration to newly-weaned, underweight pigs.

The present inventors have now synthesized a purified, water-stable immunoglobulin product that can be administered inexpensively through the water supply of animals. The product is highly effective in increasing growth and weight gain in animals.

Accordingly, it is a primary objective of the present invention to provide a composition and method for treating animals using a water-stable, immunoglobulin product based on animal plasma.

It is a further objective of the present invention to provide a composition and method for treating animals which is effective in decreasing the adverse symptoms of stress in young animals, post-weaning.

It is a further objective of the present invention to provide a composition and method for treating animals which increases growth and weight gain.

It is still a further objective of the present invention to provide a composition and method for treating animals which is convenient and economical to administer.

It is still a further objective of the present invention to provide a composition and method for treating animals which is easy and economical to manufacture.

The method and means of accomplishing each of the above objectives as well as others will become apparent from the detailed description of the invention which follows hereafter.

SUMMARY OF THE INVENTION

The invention describes a water-stable, immunoglobulin concentrate (WSIG) which improves the health and growth rate of animals at times of stress. The invention is especially effective in improving growth and reducing morbidity in young pigs, post weaning. The (WSIG) is derived from animal plasma which may be treated to separate the globulin and albumin fractions. The water-stable globulin fraction is then administered to the animals through their water system.

Treatment with the globulin significantly improves health and increases the growth and weight gain in animals, especially in underweight, stressed pigs, post-weaning. The globulin composition is inexpensive to manufacture and is easy and economical to administer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention relates to a new method and composition for improving growth and weight gain in animals through the administration of immunoglobulin in the animals' water supply. Reference is often made to the use of this invention with respect to pigs, however it is to be understood that the invention is not limited to any

particular animal. One of skill in the art can readily appreciate that the invention will be applicable to any food or companion animal.

Previous attempts at decreasing morbidity and mortality in young pigs have focused on the delivery of supplements, including immunoglobulin fortified supplements, via dry feed or milk prior to the weaning period. While moderately successful in reducing morbidity and mortality, these methods have many problems, including the expense and difficulties involved with the administration and use of milk replacement products. Further, light-end pigs do not benefit from the use of supplements administered through feed since they will consume primarily water during periods of stress post-weaning.

The present invention is predicated upon the discovery that the administration of immunoglobulins through the animals' water system is effective in increasing weight gain and growth in animals. This method is especially effective in highly stressed pigs that are weak with a reduced appetite. Further, unlike previous methods of supplementation, the present invention is especially effective in treating young, underweight pigs that are in a transitory starvation period post-weaning.

The composition of this invention is a plasma-based, substantially purified globulin concentrate. The term "substantially purified" refers to the fact that the globulin concentrate contains insufficient amounts of other substances that will cause the concentrate to clot or gel in water.

Similarly, the term "substantially free" of albumin refers to the fact that the globulin concentrate contains insufficient amounts of albumin to clot or gel when mixed in a highly concentrated form in water (>10% solution).

Also, the term "water-stable" refers to the fact that the globulin concentrate of this invention does not gel, precipitate, or clot. Instead, the water-stable product is a fluid with free-flowing solution characteristics.

Nutritional supplements, including SDAP, have generally been administered through the animal's feed or as part of milk replacement therapy. Blood plasma itself gels in water. Now, using the applicants' globulin separation method, the globulin can be administered inexpensively through the animals' water. The globulin concentrate of the present invention is stable in water, and therefore does not clog the lines of the animal's water system. Further, in contrast to spray-dried animal plasma and other feed and milk replacement supplements, Applicants' globulin concentrate does not need to be placed in the food supply numerous times per day, thereby decreasing labor costs.

The globulin concentrate of the present invention can be administered to animals during all stages of their life cycles to improve their health and nutrition, but is more effective in periods of stress, and is especially effective in young, stressed pigs, post-weaning. These pigs are usually weak from both disease and lack of appetite. The consumption of immunoglobulin from the water improves the short-term enteric health of the animal which promotes feed

and water intake. The provision of immunoglobulin in the water ensures the short-term protection of the pig's enteric health.

Swine producers can use the globulin concentrate of the present invention to improve the health and growth rates of pigs. The product is efficacious, especially in young stressed, pigs, cost-effective, and a labor saving tool in the management of pigs. The commercial applications of this invention are many and range from the use of the concentrate to more successfully wean large groups of pigs at very young ages (<10 days of age) to the administration of the product to weaned pigs in traditional swine production systems to overcome typical health challenges. Swine units have progressively grown in size and there is less management time allotted to the care of individual pigs. Health management is critical in minimizing disease outbreaks since such outbreaks are expensive in terms of medication cost and management time. This invention is successful in promoting the maintenance of enteric health by supplying an appropriate, adequate source of gastrointestinal protection to the animals.

The immunoglobulin concentrate and water delivery method is also effective in protecting the gastrointestinal health of other stressed animals, including cattle, horses, and poultry. Stress such as mild to severe starvation, shipping, surgery, socialization, corticosteroid treatment, intentional weight reduction, force molting (poultry), physical disability, and birthing, all can result in a reduction in

feed intake and breakdowns in gastrointestinal health. The opportunity for disease is decreased through the administration of the present water-soluble immunoglobulin concentrate.

The immunoglobulin concentrate of the present invention is derived from animal blood. The source of the blood can be from any animal that has blood which includes plasma and immunoglobulins. For convenience, blood from beef, pork, and poultry processing plants is preferred. Anticoagulant is added to whole blood and then the blood is centrifuged to separate the plasma. Any anticoagulant may be used for this purpose, including sodium citrate and heparin. Persons skilled in the art can readily appreciate such anticoagulants. Calcium is then added to the plasma is to promote clotting, the conversion of fibrinogen to fibrin. This mixture is then centrifuged to remove the fibrin portion.

As described above, it is the fibrin portion which combines with calcium from the water source to gel and clog water lines. Once the fibrin is removed from plasma resulting in serum, the serum can be used as a principal source of Ig. Alternatively, one could also inactivate this portion of the clotting mechanism using various anticoagulants.

In addition, one could simply inject the water-stable plasma into the water as the immunoglobulin source. Either serum or plasma may be used as an immunoglobulin souce in the globulin concentrate product. The further processing to

concentrate immunoglobulin simply ensures fewer problems with line obstruction because less protein will be injected into the line.

The defibrinated plasma is next treated with an amount of salt compound or polymer sufficient to precipitate the albumin or globulin fraction of the plasma. Examples of phosphate compounds which may be used for this purpose include all polyphosphates, including sodium hexametaphosphate and potassium polyphosphate. The globulin may also be isolated through the addition of polyethylene glycol or ammonium sulfate. For reasons of convenience and economy, the polyphosphate compounds are preferably added to the plasma in a concentration of about 0.5-1% by weight of the plasma.

Following the addition of the phosphate compound, the pH of the plasma solution is lowered to a range of between 3.5-4.5 to stabilize the albumin precipitate. The pH should not be lowered below 3.5, as this will cause the proteins in the plasma to become damaged. The preferred pH range is 3.5-4.0, with 3.95 being most preferred. Any type of acid can be used for this purpose, so long as it is compatible with the plasma solution. Persons skilled in the art can readily ascertain such acids. Examples of suitable acids are HCl, acetic acid, H_2SO_4, citric acid, and H_2PO_4. HCl is preferred, and 2N HCl is most preferred. The acid is added in an amount sufficient to lower the pH of the plasma to the designated range. Generally, this amount will range from a ratio of about 1:4

to 1:2 acid to plasma. The plasma is then centrifuged to separate the globulin fraction from the albumin fraction.

The next step in the process is to raise the pH of the globulin fraction with a base until it is no longer corrosive to separation equipment. Acceptable bases for this purpose include NaOH, KOH, and other alkaline bases. Such bases are readily ascertainable by those skilled in the art. NaOH is the preferred base, and a 10% solution of NaOH is most preferred. The pH of the globulin fraction is raised until it is within a non-corrosive range which will generally be between 5.0 and 9.0. The preferred pH range is 7.0-8.0, with 7.5 being most preferred. The immunoglobulin fraction is then preferably microfiltered to remove any bacteria that may be present.

The final immunoglobulin concentrate can optionally be spray-dried into a powder. The powder allows for easier packaging and the product remains stable for a longer period of time than the raw globulin concentrate in liquid or frozen form. The immunoglobulin concentrate powder has been found to contain approximately 35-50% IgG. The immunoglobulin concentrate is then mixed with serum concentrate and other compounds to improve wettability.

The globulin concentrate is administered to the animal by placing it in the animal's water system via a stock solution and a liquid dispenser. The globulin composition readily dissolves in water and remains stable in a highly-concentrated solution that does not obstruct the water line. While animals receive benefit from any amount of globulin

composition placed in their water source, the concentration of globulin composition in the water should be at least 0.1% by weight. The response to the product is titratable, meaning a greater response is observed with a higher concentration so much higher levels of globulin concentrate can be added. The concentration of globulin can be increased until the water becomes saturated with globulin, i.e. the globulin can no longer be dispersed within the water. Various concentrations of stock solutions and/or injection rates may be used to alter the concentration of immunoglobulin in the water.

For economy and efficiency and to achieve best results in stressed pigs, the globulin composition should be dispersed in the water in a concentration of from about 0.375 to about 3.0% by weight. The concentration of IgG in the water in this concentration ranges from approximately 0.1-0.75% by weight.

A preferred water dispenser for use with this invention is manufactured by Dosatron® and is sold as the Proportional Non Electric Liquid Dispenser. The dispenser is installed directly on the water supply line. The dispenser is activated by water pressure. As the water passes through the dispenser it takes up the designated percentage of concentrate to deliver to the animals.

The globulin concentrate can be administered to the animal at any stage of the animal's life. However, as a practical matter it will be most frequently used in young pigs prior to the stage when they begin consuming feed since

this is the group of animals that have shown the greatest response to the treatment. The concentrate is most advantageously used during times when the animals are most stressed. As already described, the globulin concentrate is especially effective in animals post weaning during the transient starvation period when they are not yet consuming feed. The animal drinks the globulin-fortified water and, with improved health, begins to eat and to drink larger quantities of the water. As the animal continues to drink, the globulins from the water help protect the animal from disease by providing additional protective support to the mucosal barrier. The additional protection helps the animal overcome the negative effects of stress, including leaky gut syndrome and diarrhea. Noticeable improvements in growth will occur with oral administration of 75 mg immunoglobulin/kg body weight or 0.5 g immunoglobulin/hd/day. However, concentrations that will provide 375 mg immunoglobulin/kg body weight or > 2.5 g/hd/day are most effective.

The globulin concentrate may also be administered with certain additives or nutrients, such as carbohydrates, vitamins and minerals, that are added to the water directly or mixed in with the concentrate prior to adding to the water. The only requirement is that the additives also be water soluble and compatible with the immunoglobulin concentrate. Such additives can be readily ascertained by those skilled in the art. An example of such a composition

is included (Table 2). This composition is then agglomerated to improve wettability.

In tests involving the globulin concentrate, the administration of the product to pigs through water reduced the frequency of medication administration and the severity of disease outbreaks.

The following examples are offered to illustrate but not limit the invention. Thus, they are presented with the understanding that various formulation modifications as well as method of delivery modifications may be made and still be within the spirit of the invention.

EXAMPLE 1

Effect of Immunoglobulin Concentrate on Young Weaned Pigs

Porcine immunoglobulin was substantially purified from porcine plasma using the previously described procedures. The porcine immunoglobulin concentrate was spray-dried and analyzed for porcine IgG content. In powder form, the product contained by analysis 45% IgG. This powder was then reconstitued with tap water and the pH reduced to approximately 4.5 with citric acid to produce a 30% w/w stock solution. This stock solution was then injected into the water line in a ratio of 1 part per 100 parts water which was used as the sole water source for 6 pens of 24 pigs/pen in the trial. The product was injected into the water line for a period of one week. The control group (six pens of 24

pigs/pen) were provided with water injected with an acidified stock solution (as above). Pig weights were measured initially and at the end of the 7 day trial period. The number of pigs medicated during the week was recorded for both the control and treated (+Ig) groups:

TABLE 1

	Control	+Ig
Body Weight (kg)		
Initial Weight	6.02	5.92
Final, d 7*	7.64	7.61
ADG, g/d	231	241
Medication,% of pigs	12.5%	4.0%

*Final body weights represent an average body weight for the pen of pigs. Pigs were removed from the pen for intensive care when necessary.

Table 2 sets forth the composition of the water-stable globulin concentrate used in the study:

TABLE 2

Ingredient	As-is, %
Serum concentrate	52.21
Immunoglobulin concentrate	24.28
Lactose	15.00
Fructo-oligosaccharide	5.00
Potassium chloride	1.66
Lecithin	1.00
DL-methionine	0.86
Total	100.0

EXAMPLE 2

Preferred Manufacturing Method For Globulin Concentrate

The following illustrates a preferred method of manufacturing the globulin concentrate of the present invention:

Plasma

↓

0.3% $CaCl_2$

↓

P-3000 Centrifuge to remove fibrin

↓

Allow any foam to dissipate
Filter sock 60 mesh

↓

Add 1% Hexameta Phosphate (granular form) by wt. to serum
This is made up as a stock solution
(1 lb to 1.7 lbs hot water) (≈ 230 lbs solution)
and added as a solution to the serum

↓

pH is adjusted to 3.9-3.96 range (3.95 is target),
with a 2N HCl solution
This is done as a slow time dependent addition
(approx 718.5 lbs/1000 gal)
After pH adjustment, allow 1 hour for reaction
completion while stirring

↓

Centrifuge Alpha Laval 717 feed rate approx 18 gal/min
To determine rate of feed and discharge, use microcentrifuge
tubes to determine solids for discharge rate
(use 10,000 g x 10 min)

Wt. Supernatant
Wt. Liquid
Determine % solids

↙ ↘

Globulin Fraction

This pH and form is stable for several days for SPC's and can be used to allow accumulation of material for spray dryer

↓

Raise pH to 7.5 with 10% NaOH (≈ 186.3 lbs) - microfiltration to remove any bacteria

↓

Dialyze 20,000 molec. wt. membranes to conductivity of 1.5 ms/cm at 12g/dl protein

Albumin Fraction

This form is stable for several days so accumulation for the spray dryer is possible

↓

Dilute thick slurry by 50% with distilled water before processing
Raise pH to 8.0 with 10% NaOH (≈ 116 lbs) slowly - Do not burn proteins
Microfiltration to remove any bacteria

↓

Dialyze (20,000 m.w. membranes) to conduction of 1.5 ms/cm at 12 g/dl protein level

↓

Concentrate and spray dry
294°C inlet and 95°C outlet

↓

Analyze spray dried powder

T.P.	Phoslip
Alb.	Phosphorus
IgG	Calcium
Chol	Na
Trig	Cl
K	

↓

Concentrate and spray dry
294°C inlet and 95°C outlet

↓

Analyze spray dried powder

T.P.	Phosphorus
Alb.	Calcium
IgG	Na
Chol.	Cl
Trig	K
Phoslip	

Having described the invention with reference to particular compositions, theories of effectiveness, and the like, it will be apparent to those of skill in the art that it is not intended that the invention be limited by such illustrative embodiments or mechanisms, and that modifications can be made without departing from the scope or spirit of the invention, as defined by the appended claims. It is intended that all such obvious modifications and variations be included within the scope of the present invention as defined in the appended claims. The claims are meant to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates to the contrary.

What is claimed is:

1.

A supplement for animals comprising:

a water miscible and stable globulin concentrate based on animal plasma.

2.

A supplement according to claim 1 wherein the globulin concentrate contains at least 15% by weight IgG.

3.

A supplement according to claim 1 wherein the concentrate is contained in a water-based solution.

4.

A supplement according to claim 3 wherein the concentrate does not gel, clot or precipitate in the water.

5.

A supplement according to claim 1 which is a dried powder.

6.

A supplement according to claim 1 which is substantially purified.

7.

A supplement for animals comprising:

water; and

a water stable globulin concentrate.

8.

A supplement according to claim 7 wherein the globulin concentrate is present in a concentration of at least 0.1% by weight.

9.

A supplement according to claim 7 which is substantially purified.

10.

A method of improving weight gain and growth, while decreasing morbidity and mortality in animals comprising:

administering a supplement to an animal through the animal's water source, said supplement comprising a water stable globulin concentrate.

11.

A method according to claim 10 wherein the supplement comprises at least 15% IgG.

12.

A method according to claim 10 wherein the supplement is administered to a pig.

13.

A method according to claim 12 wherein the supplement is administered to the pig post-weaning.

14.

A method according to claim 13 wherein the pig is underweight.

15.

A method of manufacturing a globulin supplement for animals comprising:

separating albumin from plasma to form an albumin precipitate;

stabilizing the albumin precipitate with an acid;

separating the albumin precipitate from the plasma to form an albumin fraction and a globulin fraction;

raising the pH of the globulin fraction until it is non-corrosive;

adding a phosphate compound or polyethylene glycol to the globulin fraction to precipitate immunoglobulin; and

centrifuging to separate the precipitated immunoglobulin.

16.

A method according to claim 15 wherein the phosphate compound is a polyphosphate.

17.

A method according to claim 15 wherein the phosphate compound is selected from the group consisting of sodium hexametaphosphate, sodium polyphosphate, and potassium polyphosphate.

18.

A method according to claim 15 wherein the acid is hydrochloric acid.

19.

A method according to claim 15 wherein the pH of the solution is lowered to between about 3.5 and 4.5 to precipitate the albumin.

20.

A method according to claim 19 wherein the pH of the solution is lowered to between about 3.9 to 4.0 to precipitate the albumin.

21.

A method according to claim 15 further including the step of drying the globulin precipitate to form a powder.

ABSTRACT OF THE DISCLOSURE

A water soluble globulin concentrate is described. The globulin concentrate is administered through the animals' water supply and is effective in increasing growth and weight gain in animals. The concentrate is especially effective in reducing morbidity in underweight, stressed pigs, post-weaning.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COMBINED DECLARATION AND POWER OF ATTORNEY

FOR JOINT INVENTORS

As the below named coinventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names. We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled as follows: **WATER-SOLUBLE GLOBULIN CONCENTRATE FOR IMPROVING GROWTH IN ANIMALS**, the specification and drawings of which are attached hereto.

We hereby state that we have reviewed and understand the contents of the above identified specification and drawings, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code Of Federal Regulations, Section 1.56. We further declare that no application for patent or inventor's certificate on this invention has been filed by us, our legal representatives or assigns in any country foreign to the United States of America except as identified below:

NONE.

And we hereby appoint ZARLEY, McKEE, THOMTE, VOORHEES & SEASE, comprising Donald H. Zarley, Registration No. 18,543; Bruce W. McKee, Registration No. 19,651; Dennis L. Thomte, Registration No. 22,497; Michael G. Voorhees, Registration No. 25,715; Edmund J. Sease, Registration No. 24,741; Mark D. Hansing, Registration No. 30,643; Kirk M. Hartung, Registration No. 31,021; Mark D. Frederiksen, Registration No. 31,357; Daniel J. Cosgrove, Reg. No. 36,770; Michael R. Crabb, Registration No. 37,298; Heidi Sease Nebel, Registration No. 37,719; Bruce A. Johnson, Registration No. 37,361; Wendy K. Hartung, Registration No. 39,705; and Jeffrey D. Harty, Registration No. 40,639; 801 Grand Avenue, Suite 3200, Des Moines, Iowa 50309, Telephone 515-288-3667, our attorneys to prosecute this application and to transact all business in the Patent Office connected therewith.

We hereby declare that all statements made herein are of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false

statements may jeopardize the validity of the application or any patent issued thereon.

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JAMIE SCHRUM
MY COMMISSION EXPIRES
7/21/2000